## ANTI MALARIAL DRUGS

### Plenary Presentations

Impact of drug resistance on morbidity and mortality.
Jean-Francois Trape

Factors leading to the development of antimalarial drug resistance.
Nicholas J White

Antimalarial drug policies and resistance : current issues.
Sylvia Meek

Country priorities and plans for chemotherapy for malaria control in Africa.
Oladapo Walker

Collaborations to address the challenge of antimalarial drug resistance.
Peter Bloland

### Breakout Sessions

**Programme**

1. Meeting Challenges with Antimalarial Drugs in Africa.

2. African Scientists and Institutions in Developing Drugs for Malaria.

3. Joint Session: Management of Severe Malaria and Antimalarial Drugs

**Summary Report**

## PLENARY PRESENTATIONS

### Impact of Drug Resistance on Morbidity & Mortality in Malaria Infections in Africa

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**Introduction**

Chloroquine-resistant strains of *P. falciparum* were first observed during 1978 in East Africa. Between 1978 and 1988, resistant parasites have been reported in all countries of tropical Africa. In each newly affected country, chloroquine resistance has progressed in three different ways: (1) it has spread in a growing number of locations and regions in the country; (2) the prevalence of resistant strains in each area has increased; (3) the degree of resistance has intensified, with a relative reduction in RI type responses in favour of RII and RIII type responses. Despite high levels of resistance, chloroquine remains in 1999 the first line treatment for malaria attacks in most African countries. A number of studies have reported that patients infected with resistant strains improved clinically within a few days when receiving chloroquine, and this has lead to the assumption that chloroquine retains sufficient efficacy to justify its use even though a high proportion of children remain parasitemic after treatment. In this paper, we review hospital and community-based studies conducted in Africa over the past fifteen years. There is now clear evidence that chloroquine resistance has had a dramatic impact on morbidity and mortality in malaria infections in Africa.

**Hospital-based studies**

The first evidence of increasing malaria morbidity and mortality temporally related to the emergence of chloroquine resistance came from National health statistics of hospital admissions and deaths in Malawi. During the period 1978-1983, the incidence of admissions for malaria among children under 5 years of age more than doubled, with the case fatality rate remaining relatively constant and averaging 5% (Khoromana *et al.*, 1986). Case reports of chloroquine prophylaxis failure in nonimmune visitors to Malawi had substantiated local emergence of resistant *P. falciparum* during this period (Overbosch *et al.*, 1984; Fogh *et al.*, 1984), and studies among Malawian children conducted in 1984 at six surveillance sites indicated that on average 57% of children were parasitemic on Day 7 after standard malaria therapy with chloroquine (Khoromana *et al.*, 1986).

A second evidence came from a study by Greenberg *et al.* (1989) in Zaire. This study was conducted at Mama Yemo Hospital, which was the largest medical centre in Kinshasa and served as a referral centre for patients with severe malaria who have not responded to antimalarial therapy either at home or at one of the many clinics in the city. From 1982 to 1986, the total number of paediatric admissions and deaths remained relatively constant, but the proportional malaria admission rate increased significantly from 29.5% in 1983, 41.7% in 1984 and 45.6% in 1985 to 56.4% in 1986, and the proportionnal malaria mortality rate, from 4.8% in 1982, 7.0% in 1983, 7.9% in 1984 and 8.9% in 1985 to 15.3% in 1986. During this period, there were no significant changes in diagnostic capabilities or in medical personnel at the hospital that could account for the results. However, chloroquine-resistant *P. falciparum* malaria emerged in Kinshasa during the 5-year study interval. In 1982, no case of *in vivo* or *in vitro* chloroquine-resistant malaria was detected in Kinshasa (Nguyen-Dinh *et al.*, 1985). The first evidence of *in vivo* chloroquine resistance in the city was observed in 1984 (Ngimbi *et al.*, 1985), and by 1985 a total of 56% of *P. falciparum* infections in Kinshasa children were not cured by a standard regimen of 25 mg/kg chloroquine (Paluku *et al.*, 1988). By 1986, a total of 82% of *P. falciparum* parasites isolated from children at Mama Yemo Hospital exhibited *in vitro* resistance to the drug (Nguyen-Dinh *et al.*, 1987).

Chloroquine resistance emerged in Congo in 1985 (Carme *et al.* 1990). In December 1985, 39% of Brazzaville children were not cured by 25 mg/kg chloroquine. Trends in the incidence of malaria admissions and cerebral malaria deaths in the four hospitals of Brazzaville during the period 1983-1989 were studied by Carme *et al.* (1992a). From 1983 to 1986, malaria

admissions increased from 22% to 54% of total paediatric admissions and stabilized the following years. Cerebral malaria deaths more than doubled during the period 1986-1989 compared to the period 1983-1985.

During the period 1986-1988, an upsurge of malaria-related convulsions was observed in the paediatric emergency room of Calabar Hospital, Nigeria, and the number of cerebral malaria cases more than doubled (Asindi *et al.*, 1993). The increase in the incidence of cerebral malaria corresponded to the emergence of chloroquine resistance in this area of Nigeria. A high proportion of children (81%) who were hospitalized in 1988 for malaria-related convulsions did not respond to chloroquine.

After the emergence of chloroquine resistance, a study in a district hospital in Kenya indicated that among children hospitalized for malaria, the risk of dying was associated with the antimalarial treatment received. Children who received treatment with a regimen that would clear parasitaemia (either sulfadoxine-pyrimethamine, quinine, or a five days of sulfamethoxazole-trimethoprim) had a 11% case fatality rate within 8-weeks of hospitalization compared with a 33% case-fatality-rate among children who received chloroquine (Zucker *et al.*, 1996). Because of the striking effect of treatment on survival from malaria, sulfadoxine-pyrimethamine was provided as first line therapy of children admitted to that hospital with malaria beginning in February 1992. The case-fatality rates decreased from 9.9% in 1991 to 5.1%, 3.6%, and 3.3% in 1992, 1993, and 1994, respectively (Zucker *et al*, unpublished).

In absence of malaria treatment, anaemia is a frequent complication of *P. falciparum* attacks in young children. In the past, severe malarial anaemia was the leading cause of malaria deaths in areas of central Africa with limited access to antimalarial drugs (Kivits, 1951), but its incidence decreased considerably when chloroquine became widely used (Trape *et al.*, 1987 and unpublished). Since the 1980's, numerous studies have reported a high incidence of severe malarial anaemia among hospitalized children, and most of these studies were conducted in areas with high levels of chloroquine resistance. In Banjul, The Gambia, a prospective study of 9584 consecutive paediatric admissions to the Royal Victoria Hospital was conducted over 3 years, from 1988 to 1990, when chloroquine resistance was emerging. During the study, there was a 27% annual increase in severe anaemia owing to malaria (Brewster & Greenwood, 1993). In Western Kenya, severe anaemia has become a major cause of malaria death in young children after the emergence of chloroquine resistance, and the risk of dying from severe malarial anaemia was significantly higher for children treated with chloroquine than for children receiving other antimalarials (Zucker *et al.*, 1996).

**Population studies**

In Senegal, long-term demographic surveillance programmes were initiated in three rural areas of the country between 1963 and 1984. Since 1984, a continuous study of the causes of death has been added to the registration of demographic events and specific data on malaria have been collected in each area (Sokhna *et al.*, 1997; Trape *et al.*, 1998). These programmes were conducted in Mlomp (rain forest, 11 villages, 7,287 inhabitants in 1995), Niakhar (Sahel, 30 villages, 28,246 inhabitants in 1995), and Bandafassi (Sudan savanna, 38 villages, 8,612 inhabitants in 1995). All deaths which occurred among the three study populations were investigated using the verbal autopsy technique and available data from medical source. Levels of chloroquine-resistance were determined by *in vivo* tests and over twelve years, from 1984 to 1995, malaria specific mortality was studied prospectively. The first therapeutic failures with chloroquine were observed in 1990 in Mlomp, in 1992 in Niakhar, and in 1993 in Bandafassi. The following years, standardised surveys documented the intensification of chloroquine resistance. High levels of chloroquine resistance appeared rapidly in Mlomp (RII/RIII: 36% in 1991, 30% in 1992, 41% in 1994, 46% in 1995). Chloroquine resistance progressed less rapidly in Niakhar (RII/RIII: 10% in 1993, 15% in 1994, 17% in 1995, 29% in 1996) and in Bandafassi (RII: 6% in 1994, 16% in 1995). The emergence of chloroquine resistance has been associated with a dramatic increase in malaria mortality in each of the studied populations (Trape *et al.*, 1998). In Mlomp, where malaria was hypoendemic and child mortality was low as a result of the widespread use of chloroquine for prophylaxis and treatment and important health programs, malaria became mesoendemic and the incidence of malaria deaths in

children under ten has risen 5.5 fold. The increase in malaria mortality was particularly dramatic among children under five, with 0.5, 3.4 and 5.5 deaths per thousand children per year for the periods 1985-1989, 1990-1992 and 1993-1995, respectively. In Bandafassi, a holoendemic area where access to health care was limited, mortality attributable to malaria in children under five has risen 2.5 fold, from 4.2 to 11.4 per thousand per year for the periods 1984-1992 and 1993-1995, respectively. In Niakhar, a mesoendemic area, where malaria transmission was the lowest of the three study areas, mortality attributable to malaria in children under ten has doubled, from 4.0 to 8.2 per thousand per year for the periods 1984-1991 and 1992-1995, respectively.

Except in Senegal, studies of malaria mortality at the community level in Africa either have been short term or were initiated after the emergence of chloroquine resistance. In a site in a rural area of coastal Tanzania where mortality rates and causes of death were investigated during the years 1984-1985 and 1992-1994, overall child mortality remained unchanged between the two surveys despite the introduction of a sucessful immunization programme and a village health system. The proportion of deaths attributed to malaria was 2-fold higher during the most recent study (Mtango & Neuvians, 1986; Premji *et al.*, 1997).

**Indirect malaria mortality and impact on diseases other than malaria**

In most areas of tropical Africa, chloroquine chemoprophylaxis is now poorly effective for preventing *P. falciparum* infections during pregnancy. Malaria in the pregnant women increases the risk of low birth weight which represents the greatest single risk factor for neonatal and early infant mortality (Jelliffe, 1968; McGregor *et al.*, 1983; Brabin, 1991; McCormick, 1985). This suggest that chloroquine resistance may also have resulted in higher levels of infant mortality through decreased efficacy of chemoprophylaxis recommanded to pregnant women (Steketee *et al.*, 1996).

It has been a general observation from malaria control programmes through DDT spraying, impregnated bednets and chemoprophylaxis that effective malaria control may prevent more deaths than the number of deaths previously attributed to malaria in the same population (Najera & Hempel, 1996). One reason is the contribution of the health services, created or improved for malaria control, to the management of other health problems as well as to the general health information and education of the population. However, another probable factor is that malaria affects the capacity of the organism to resist concomitant diseases. It has been shown that drug resistance is an important factor in producing anaemia or preventing optimal haematologic recovery in children receiving non-effective malaria treatment (Bloland *et al.*, 1993; Slutsker *et al.*, 1994). It is likely that the case-fatality of certain diseases increases in the presence of malaria-associated anaemia which is related to the intensity and duration of parasitaemia (Greenwood, 1987; Bradley-Moore *et al.*, 1985)

Blood transfusions are widely used in referral hospitals to treat severe anaemia, and this is likely to constitute a cause of HIV contamination of young chidren. The association between malaria, blood transfusions, and HIV seropositivity was investigated in Kinshasa by Greenberg *et al.* (1988). Malaria was the most frequent indication for blood transfusions in both hospitalized and emergency ward pediatric patients. The emergence of chloroquine resistance was associated to a 2-fold increase of the number of blood transfusions, and a strong positive association between transfusions and HIV seropositivity was detected. Compared with children who received no transfusion, children who received one transfusion were 2.8 times as likely to be HIV seropositive, those who received two transfusions were 7.9 times as likely to be HIV seropositive, and those who received three transfusions were 21.9 times as likely to be HIV seropositive.

For most African countries, there are no national data on causes of death. However, information on the levels and trends of overall child mortality are often available at the national level from surveys and censuses. In the case of Senegal, the risk that a new born child die before the age of 5 declined to 287, 236, 191 and 131 per thousand during the periods 1971-1975, 1976-1980, 1981-1986, and 1988-1992, respectively (Pison *et al.*, 1995). By contrast, the most recent survey indicated that child mortality was 139 per thousand during

the period from March 1992 to March 1997. This change in the national trend was concomitant with the generalization of chloroquine resistance in the whole country, and the increase in malaria mortality observed among three rural study populations, an indication that the recent stop in the decrease of child mortality in Senegal could be related to chloroquine resistant malaria (Trape *et al.*, 1998). In The Gambia, data from population censuses and various other sources showed rapid secular improvements in mortality among those younger than 5 years from the late 1960s to the late 1980s; however, as in Senegal, overall mortality stabilized or even increased in the early 1990s when chloroquine resistance emerged (Hill *et al.*, 1998). Demographic and health surveys in Ivory Cost and Central African Republic indicate similar trends.

**Discussion**

There is now strong evidence that the emergence and spread of chloroquine resistance has had dramatic public health impact in Africa. Malaria specific mortality has probably doubled or more in most parts of tropical Africa, and it is likely that increased malaria-related anaemia has had significant effects on mortality from other diseases and contributed to HIV dissemination among children. Such dramatic impact was considered as certain by most experts in the 1970's and early 1980's, i.e. before the emergence and spread of chloroquine resistance, and was rapidly confirmed by a hospital-based study in Kinshasa (Greenberg *et al.*, 1989). However, by contrast, many subsequent studies in Africa concluded there was no urgent need to change national policies for the treatment of malaria from chloroquine to alternative drugs.

We believe that two main factors have long masked the real impact of chloroquine resistance. First, only limited data from prospective mortality studies were available. Althought several dozens of community studies of malaria mortality have been conducted in Africa (see review in Snow & Marsh, 1995, and Snow *et al.*, 1999), most of them have been short term and only those conducted in Senegal have collected data in the same community before, during and after the emergence of chloroquine resistance. The number of hospital-based studies which documented the impact of chloroquine resistance was also limited. Second, by contrast, a number of *in vivo* studies of chloroquine efficacy were carried out. With the progression of chloroquine resistance, these studies indicated that an increasing number of patients treated with chloroquine did not clear their parasitaemia, but also that severe complications were rarely seen. Since most patients improved clinically within a few days even in case of parasitological failure, this has lead to the assumption that chloroquine retains sufficient efficacy to justify its use even though a majority of patients remain parasitaemic (Brandling-Bennett *et al.*, 1988; Bloland *et al.*, 1993).

To explain this paradox, it is necessary to consider the potential lethality of each malaria attack occuring among patients living in highly malaria endemic areas. The daily surveillance of cohorts of children in Congo and Senegal has shown that most individuals suffer several dozens of malaria attacks during childhood (Trape *et al.*, 1987; Trape & Rogier, 1996). Over one year, a cohort of 1,000 children aged 0-5 years present about 2,000 to 4,000 malaria attacks according to the entomological inoculation rate. Even when malaria mortality is high, e.g. ten per thousand children per year (as observed in populations with poor access to antimalarials or high levels of chloroquine resistance), this implies that the potential lethality rate of each malaria attack remains very low, since the 990 surviving children totalize from 1,980 to 3,960 malaria attacks during this given year. In the case of the Mlomp study in Senegal, analysis of demographic, epidemiological and clinical data suggested that only one malaria attack in five hundred was lethal in children under five years old after the emergence of chloroquine resistance despite an eleven-fold increase in malaria mortality in this age-group due to chloroquine resistance. The low lethality of malaria attacks under conditions of high endemicity explains why severe complications occur rarely during *in vivo* tests, even when they are conducted among young children and using poorly effective drugs. Furthermore, for evident ethical reasons, most *in vivo* studies of chloroquine efficacy in Africa were carried out under close surveillance among either asymptomatic subjects, or patients belonging to age-groups not exposed to high malaria mortality, or selected children with mild or very mild malaria symptoms.

Since the early 1950's, chloroquine has saved the life of dozens of millions of Africans. There is now strong evidence that the spread of chloroquine resistance has a dramatic public health impact, with many children dying each year because of the use of chloroquine for malaria treatment. There is an urgent need to change treatment policies in Africa.

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# [1]Preventing Antimalarial Drug Resistance

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**Introduction**

The estimated annual mortality from malaria ranges between 0.5 and 2.5 million deaths. The burden of this enormous death toll, and its concomitant morbidity, is borne by the world's poorest countries. It has been said that 90% of the deaths from malaria in the world occur in Africa. Malaria morbidity and mortality in the tropical world have been held in check by the widespread availability of cheap and effective antimalarial drugs. We are now losing these valuable drugs to resistance, and this may represent the single most important threat to the health of people in tropical countries. Chloroquine has been the mainstay of antimalarial drug treatment for the past forty years, but resistance is now widespread throughout the continent of Africa and elsewhere. Few tropical countries are unaffected. Pyrimethamine-sulphadoxine (PSD) is usually the next choice after chloroquine. Both these antimalarials cost less than 20 cents per adult treatment course, but the drugs required to treat multi-drug resistant falciparum malaria (quinine, mefloquine, halofantrine) are over ten times more expensive and these cannot be afforded by most tropical countries - especially those in Africa. Resistance to PSD is increasing, particularly in East Africa. As treatments lose their effectiveness, morbidity and mortality from malaria will rise further. Can this be prevented? Can we really "roll back malaria"?

The rationale for combining drugs with independent modes of action to prevent the emergence of resistance was developed first in anti-tuberculous chemotherapy. The same principle has since been adopted in cancer chemotherapy and, more recently, in the treatment of AIDS and early HIV infection. Now it would not be considered ethical to treat tuberculosis or AIDS with a single drug. The same should apply to the treatment of malaria. This reflects the opinions of many leading researchers in the field of malaria chemotherapy. The principle is simple. Resistance arises from chromosomal mutations in the malaria parasite. The chance that a mutant will emerge that is simultaneously resistant to two different antimalarial drugs is the product of the per parasite mutation rates for the individual drugs, multiplied by the number of parasite[1]s in an infection that are exposed to the drugs. For example if 1 in $10^9$ parasites are resistant to drug A and 1 in $10^{13}$ are resistant to drug B, and the genetic mutations which confer resistance are unlinked, then only 1 in $10^{22}$ will be resistant simultaneously to both A and B. Most patients ill with malaria have between $10^8$ and $10^{12}$ parasites at presentation, and a biomass of $>10^{13}$ parasites in a single person is physically impossible. In this example therefore, the majority of patients will have at least one parasite resistant to drug A, between 0.1 and 1% will have a parasite resistant to drug B, but a parasite resistant simultaneously to the two drugs would only occur approximately once every $10^{12}$ treatments (i.e. less than once a century). Thus compared with sequential use of single drugs (current policy), combinations will considerably retard the development of resistance.

Artemisinin and its derivatives (artesunate, artemether, dihydroartemisinin) are the most potent and rapidly acting of all the antimalarial drugs. They reduce the number of infecting malaria parasites by approximately 10,000-fold per asexual (two day) life cycle compared to 100 to 1,000-fold for other antimalarials. Artemisinin and its derivatives are remarkably well tolerated and, so far, no significant resistance has been reported either in clinical isolates or in laboratory experiments. Combinations of artemisinin, or one of its derivatives, with mefloquine or lumefantrine (benflumetol) have proved highly effective even against multi-drug resistant *Plasmodium falciparum* . Combinations achieve cure rates even higher than long courses of artemisinin derivatives used alone. On the North-Western border of Thailand, where the most drug resistant *P falciparum* in the world are found, the systematic use of

[1] This presentation draws heavily on the opinions of several leading authorities, presented in the recently published: White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, Kokwaro G, Ouma J, Hien TT, Molyneux ME, Taylor T, Newbold CI, Ruebush II TK, Danis M, Greenwood BM, Anderson RM, Olliaro P. Averting a malaria disaster. *Lancet* 1999; 353:1965-7.

combination chemotherapy has halted the progression of mefloquine resistance. This has been attributed to two factors. First, combinations ensure high cure rates because three day's treatment with an artemisinin derivative eliminates most of the infection, and the relatively small residuum of parasites remaining is exposed to maximum concentrations of the more slowly eliminated mefloquine. This residuum (a maximum of $10^5$ parasites or 0.000001% of the asexual parasites present initially) is all [2]that is exposed to mefloquine alone. Thus because of this rapid reduction in the parasite population within each patient, the selective pressure for the emergence of mutants with reduced mefloquine sensitivity is lessened considerably. Any mefloquine resistant mutants arising in the initial infection would be expected to be eliminated by the artesunate. Second, the artemisinin derivatives reduce gametocyte carriage by approximately 90%. Recrudescent (i.e. resistant) infections are associated with increased gametocyte carriage rates which provides a powerful selection pressure to the spread of resistance. In Thailand, an infection which recrudesces after mefloquine treatment is four times more likely to have patent gametocytaemia than a successfully treated infection. This transmission advantage is prevented by the combination with an artemisinin derivative. These benefits are particularly important in areas of low or unstable transmission where morbidity and mortality are high, and most malaria is treated (as opposed to asymptomatic and therefore not treated). In this epidemiological context the antimalarial drugs are under intense selective pressure and resistance has, in the past, often developed rapidly. In high transmission areas, where infections occur frequently, and are usually asymptomatic in older children and adults, the rapidly eliminated artemisinin derivative will not be able to protect its more slowly eliminated partner during the elimination "tail" of declining blood concentrations. Infections newly acquired during this "tail" will therefore be under selection pressure. But provided the patients with these infections are treated with the combination if they become symptomatic, and provided the combination partner retains some efficacy against any selected mutants, they will usually be cured, and the resistant parasites will not be transmitted. If the infection does not recrudesce to symptomatic levels of parasitaemia, then it is much less likely to develop patent gametocytaemia - and it will not, therefore, be transmitted. The reduction in the risk of selecting resistance in the primary symptomatic infection is not affected by the prevailing level of malaria transmission. Thus we believe that combinations should slow the evolution of drug resistance in all malarious areas. There are additional, and potentially important, benefits to artemisinin combinations. The rapid therapeutic response ensures that patients are able to return to school or work earlier and, even in the unlikely event of complete resistance to the combination drug (in this case mefloquine), a therapeutic response will still occur, i.e. there will not be a high-grade or dangerous failure to respond to treatment.

Our current practice is to deploy antimalarial drugs individually in sequence. When one fails, another is introduced. Unfortunately there are few antimalarials and the evolution of resistance in *Plasmodium falciparum* appears to be faster than the development of new drugs. There are compelling reasons to believe that resistance to the available antimalarial drugs would be slowed or prevented by the addition of artemisinin or one of its derivatives, as has been the case with mefloquine. Combining an artemisinin derivative with chloroquine and PSD in areas where partial sensitivity to these compounds is still retained should extend their useful life.

## Several concerns with this approach are now discussed

### Will resistance to the artemisinins be encouraged?

If the artemisinin derivatives are so effective in the management of severe malaria then maybe they should be withheld from use in uncomplicated malaria in those areas "where they are not needed", in order to protect them from the development of resistance. However, combination chemotherapy **does** protect the artemisinin derivatives from the development of resistance. If the drugs are always deployed in combination with another, unrelated,

antimalarial then, provided they are at least partially susceptible to the second drug, parasites are never exposed to the antimalarial activity of the artemisinin derivative alone. Furthermore, given the reassuring lack of resistance to date, and the rapid elimination of these drugs such that sub-inhibitory (i.e.selective) blood or plasma concentrations occur for only hours. Parasites either see maximum concentrations -or none at all! It is reasonable to conclude that resistance to this group of drugs will develop relatively slowly . Furthermore artemisinin derivatives are already now widely available in many tropical countries, and their use is usually regulated poorly. This is already providing selective pressure to the emergence of resistance. If these drugs were deployed only in combination with other antimalarials, then artemisinin resistance would develop much more slowly. This mutual protection will result in a considerably longer useful life span for both components in combination antimalarial chemotherapy than if the two components were deployed in sequence. Resistance could be delayed by decades.

**Will the cost be prohibitive?**

Cost is usually the major factor determining the deployment and use of antimalarial drugs. Many recent cost estimates for the artemisinins have been inflated. Combinations with artemisinin derivatives would, in general, be expected to double the individual patient treatment cost. But increased short term costs should result in overall savings over the longer term. If combination treatment results in a 3 - 5 year extension in the useful lifespan of chloroquine, amodiaquine or PSD (as it has done for mefloquine on the western border of Thailand), then the overall cost would be less than that of deploying the next, more expensive, alternatives (mefloquine, quinine). Many believe resistance would be delayed by much longer if the policy were implemented immediately. As chloroquine and PSD are already failing in many areas, combination treatment would be expected to improve cure rates with a reduction in the morbidity (and thus costs) associated with treatment failure. In areas of low transmission use of the artemisinin derivatives may have the added benefit of reducing the incidence of malaria. In areas of Vietnam and Thailand where these drugs have been deployed there has been a marked reduction in the incidence of falciparum malaria saving both lives and money.

**What about toxicity?**

In experimental animals intramuscular injections of the oil-based compounds arteether and artemether have induced an unusual and selective pattern of damage to certain brain stem nuclei [12]. This appears to arise from sustained exposure of the central nervous system as a consequence of the very slow absorption of these drugs from the intramuscular site. In contrast, in these experimental animals, the therapeutic ratio is considerably larger after oral administration of these drugs, and, for the water soluble drugs, by any route of administration. This appears to be related to the rapid absorption and elimination after oral administration. There has been no evidence of any adverse neurological effects in a clinical experience extending to several million patients, detailed prospective studies in over 10,000 patients, and neurophysiological evaluations in over 300 subjects who have received multiple treatment courses.

The artemisinin derivatives are remarkably well tolerated antimalarials but combining drugs may lead to unexpected adverse effects. There is no evidence for untoward adverse effects resulting from combinations of artemisinin derivatives with mefloquine, lumefantrine, and in a small study with atovaquone-proguanil. However studies of pharmacokinetics and tolerability are needed on combinations with other available antimalarials (particularly chloroquine, PSD and amodiaquine) and these are now being undertaken. Studies are also needed on the safety of combinations in pregnancy.

**What are the Regulatory requirements?**

To ensure compliance with drug combinations, the individual components should ideally be formulated together in a single tablet or liquid preparation, but this will necessitate expensive pharmacokinetic, pharmaceutic and toxicological studies required for regulatory approval - and who will pay for these? A less satisfactory but simpler alternative would be to combine

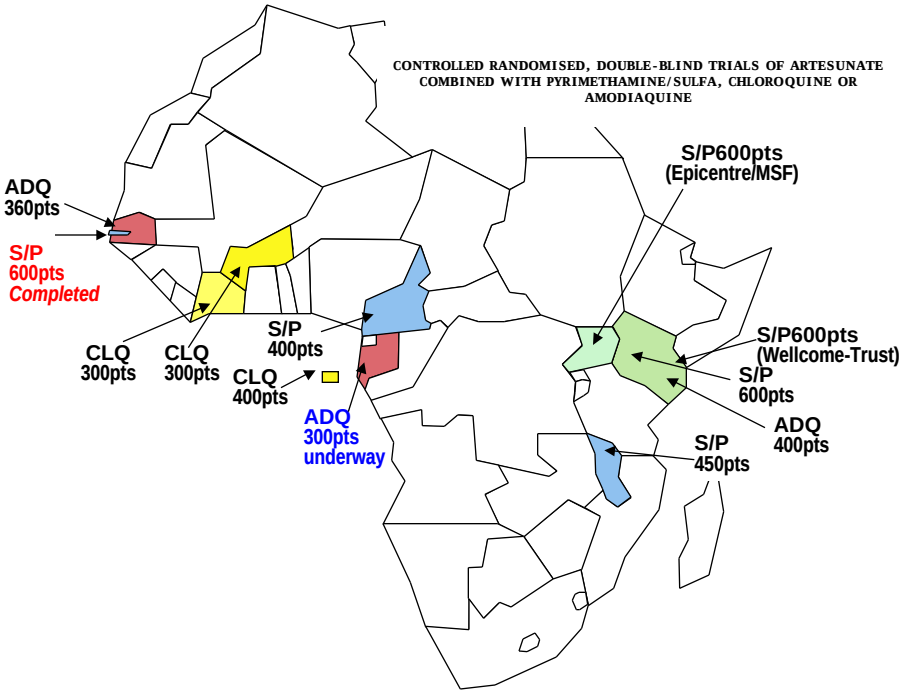
separate components in blister packs as in the multiple drug treatment of tuberculosis and leprosy. The successes of directly observed therapy (DOTS) in these infections may be relevant to antimalarial treatment. The use of combinations should be accompanied by new initiatives to facilitate compliance and to encourage dispensers and shopkeepers to educate their patients on the need to complete a full course of treatment. Wherever possible treatments
hould be observed. More effective surveillance should also be encouraged in tropical countries, both to monitor efficacy and also to document adverse reactions.

**What is to be done?**

Normally the answer is "more research", and indeed some more research is required as outlined below but, critical decisions often need to be taken with incomplete knowledge. Time is running out in Africa; four countries (Malawi, Kenya Botswana and South Africa) have already been forced to deploy PSD as their first line antimalarial. When this happened in South East Asia high level resistance developed within a few years and mefloquine had to be substituted. For the vast majority of people on the African continent who cannot afford a dollar or more for antimalarial treatment, widespread resistance to PSD or its analogues will be a disaster. Time is running out. In East Africa parasites with up to three mutations in the DHFR gene, conferring antifolate resistance, are already prevalent in some areas. Aquisition of the 164 DHFR mutation, found in SouthEast Asia, would render PSD ineffective. The development of artemisinin resistance would also be a health care catastrophe. Both these disasters could well be averted if the approach outlined in this presentation were to be adopted widely. Buying another five or ten years extra-life for the available affordable antimalarial drugs will allow time for new drugs to be developed and other interventions to be deployed. There are formidable logistic and political barriers to rapid action on the scale required, but many believe that this is now the single most important issue for malaria in Africa.

**What is being done?**

The Wellcome Trust and the World Health Organisation are funding a series of studies to determine the safety and efficacy of artemisinin derivative containing antimalarial combinations. In Southeast Asia the Wellcome Trust has supported large and detailed studies which have confirmed the safety and efficacy of artesunate (3 days) plus mefloquine combinations and the new fixed dose artemether-lumefantrine combination in the treatment of multidrug resistant falciparum malaria. Studies are underway evaluating artesunate-atovaquone-proguanil. In Africa Wellcome Trust supported studies of artesunate-SP combinations are about to start in Kenya, and it is hoped that studies of chlorproguanil-dapsone-artemisinin derivative combinations will be evaluated soon. The newly formed WHO TDR Task Force on Drug Resistance and Policies is organising large studies across the continent evaluating artesunate/chloroquine, artesunate/amodiaquine, and artesunate/SP combinations in a variety of different drug resistance and transmission intensity settings. This large programme is supported by USAID. It is hoped that by mid 2000 the results of these studies will be available and policy decisions can then be made. Research aimed at optimising the clinical and laboratory assessment of resistance, and also how the research findings can be translated into policy is also underway. Following these studies large evaluations of the impact of combinations on resistance will be conducted as the policy is, hopefully, implemented.




**Location of African combination study sites as of March 1999**.
CLQ= chloroquine versus artesunate-chloroquine, S/P = sulphadoxine/pyrimethamine vs one day artesunate + S/P vs three days artesunate + S/P, ADQ = amodiaquine versus artesunate-amodiaquine. Several studies are jointly supported.

## Antimalarial Drug Policies and Resistance : Current Issues

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**Introduction**

The purpose of this presentation is to highlight some of the key operational issues related to treatment policy and drug resistance. I subtitled this presentation "A story of ifs and buts" and I think anyone who has been involved in developing treatment policy will understand that sub-title.

A major problem that we are currently facing is that rapidly spreading drug resistance is causing a huge additional burden of disease. Many people in Africa are receiving inadequate treatment for malaria, despite the fact that several very effective drugs exist. So the challenge is how can we ensure that malaria patients receive the most effective treatment that is available and affordable?

**Drug Policy Framework**

In formulating treatment policies, the first dilemma that we face is that there is more than one goal, and these goals conflict to some extent. The primary goal obviously is to treat the patient effectively, at the very least to remove signs and symptoms, but ideally to clear all the parasites. However, there are important secondary goals, including avoiding the development of drug resistance, and if possible reducing transmission in some areas.

Looking at the context for developing a drug policy, it is dominated in many ways by the issue of access. Obviously the choice of the best drug is critically important, but this is only one element of providing treatment. In most developing countries, 50-90% of households buy drugs in the private market, and there is an interesting example from Tanzania showing that 86% of deaths occurred at home and 46% of deaths occurred without any previous access to health facilities. In the private sector there are major problems with under-dosing, irrational treatment and choice of drugs, poor drug quality and incorrect use of drugs. These are all very common and this limits significantly any policy that only addresses the public sector.

The behaviour of the patient or the carer is another important issue. A mother has to make numerous decisions when her child gets sick with malaria, and understanding this process better is essential for developing a policy that is actually implementable. She must recognise the illness, decide what action to take, how much to spend and then if that first line does not work, go through the whole process again, maybe several times, and possibly each time with the child getting sicker and therefore more costly to treat. A related issue that strongly influences policy implementation is the behaviour of the health care providers,

I will not to go into the detail of the numerous elements that need to be considered when developing and implementing a treatment policy, but I would like to give a sense of the complexity and the number of different people involved in the process. A sound legislative and regulatory framework is required, and then there is the issue of selecting which drugs are going to be in the policy, issues of procurement and distribution, the quality of drugs, and the need for countries to develop the capacity for quality control. Good information systems are crucial not only for providing data on which to base a policy, but also to monitor and evaluate the outcomes of a new policy. Linkages between different parts of the health system and decentralising the responsibilities of districts are very important. Financial management is obviously a major consideration. Public awareness and disseminating information on a new policy is essential and is quite a costly business, requiring training of health workers, in both the public and private sectors. Integrated Management of Childhood Illness (IMCI) is having quite an important influence on treatment policy in a number of countries. Negotiations with the drug procurement people must take place to get new drugs onto the essential drugs list. Then there are special conditions like epidemic situations and drugs in pregnancy, which have to be taken into account, as well as the question of unified versus targeted policies for

different groups. If there is a wide variation in levels of resistance in a country - does it make sense to have different policies for different parts of the country or is that logistically too burdensome, especially if drug resistance is developing relatively fast?

Attention also needs to be given to the mechanism of developing the policy process and who should be making the policy decisions. In the end it is a national responsibility, but the dilemmas facing national programme managers are complex and they are increasingly asking for advice and information from outside. Obviously international bodies have a major role in giving advice on treatment policy, and the extent to which guidance can be given to countries is something that needs more action. Regionally, the role of private companies is essential and much work is going on now to give guidance to countries. At country level there are obviously many different players involved in the policy development process.

Some of the major difficulties in setting policy are noted here. Firstly, there is an alarming lack of information. Obviously a policy needs to be as evidence-based as possible, but there are many unanswered questions and gaps in our information, forcing people on occasions to make decisions without enough evidence, because decisions have to be made here and now. Perhaps more thought needs to be given to systematic ways of intensifying the collection of that evidence.

Then the two important goals of the policy, effective treatment on one hand and avoiding the development of drug resistance on the other, suggest in some ways conflicting and different approaches. For convenience, ease of treatment and good compliance rates, a single dose, long half-life drug will often be more practical. In order to avoid the development of resistance, however, short half-life drugs, are preferable and these need longer treatment courses, with associated problems of compliance. Obviously with these conflicts, compromise is needed, slowing down the decision making process. Although there are some effective drugs available, none of them is ideal, and each has disadvantages. The question is how can we speed up the process of making the best drugs available and avoiding unnecessary deaths, and can this be done without unacceptable costs in terms of future resistance development?

Obviously the importance of prolonging the useful life of antimalarials by delaying resistance is clear, but then there is also the question of who benefits from the strategy if the best drugs are limited and used unofficially; limited by their cost only to those who can afford them. By the time they get into public use several years later, resistance is already developing which means that it is not the poorest people who are going to benefit. Anne Mills mentioned earlier that in terms of cost effectiveness at fixed levels of resistance the early change from chloroquine to sulfadoxine-pyrimethamine (SP) is very cost effective. Allowing for changes in resistance may be optimal, but then we can't predict the rates of resistance development.

In the past, the classical sequence for a change in first line drug has been to go from chloroquine to SP, but it might be questioned if this really is the best option. Resistance to SP develops very quickly, as has now been seen in Tanzania and Kenya. SP also produces very high density and prevalences of gametocytes, and the issue of what this may do to transmission rates in areas of lower transmission is worth considering. The use of SP for intermittent presumptive treatment of malaria in pregnant women has shown very good results, prompting the need to consider whether SP should be saved for pregnant women, as there are so few alternatives available.

Issues of cost, cost effectiveness and financing mechanisms are major determining factors. The costs of some of the common antimalarials obviously vary substantially from country to country, but average comparative prices are given here.

| **Adult dose** | **US$ average (1995)** |
|---|---|
| Chloroquine | 0.13 |
| Sulfadoxine-pyrimethamine | 0.14 |
| Amodiaquine | 0.20 |
| Mefloquine | 4.59 |

| | |
|---|---|
| Oral quinine | 2.68 |
| IV Q 1st dose | 0.47 |
| IV Q per day | 0.71 |
| Malarone | free/ c.40 |
| LapDap (predicted) | 0.25 |

The cost of changing first line drugs is very high and this may strongly influence how often countries can consider changing policy. This includes the costs of consensus building, dissemination of change, producing guidelines, and adapting supplies, which are very burdensome processes. It was calculated in Malawi for instance, that the process may have cost more than half a million dollars. So it might certainly be questioned whether it is worth going through this change for a drug which is not going to last very long.

Regarding the financing of antimalarial drugs, pharmaceuticals in developing countries consume a very high percentage of the total public and private health spending (estimated between 25-66%) and much lower in richer countries (estimated 10-15%). A strategy to achieve as much equity as possible is therefore required. Different strategies to be considered include public financing, health insurance, user charges, voluntary funding, donor financing and development loans. This needs to be worked out carefully, especially if we are moving towards the use of combination drugs.

The role of the private sector is obviously extremely important, both as a manufacturer and supplier of treatment. Companies have much to offer in terms of favourable pricing structures, provision of expertise and support for local formulation of drugs. Policy makers must take the private sector fully into account and consult with them.

The development of strategies for monitoring and evaluation is another issue. Attempts at the routine monitoring of drug efficacy have only started recently in Africa. There have been many *ad hoc* tests in different locations, but in the last few years, good progress has been made in introducing more standardised approaches, with particular support from AFRO and CDC. Some parts of Africa are better covered by systems of routine monitoring than others. The East African Network for Monitoring Antimalarial Treatment Efficacy (EANMAT) is a very good model that other areas may be interested to emulate. However, the numbers of tests carried out are small and the tests are very labour intensive. More research is needed on monitoring resistance through routine health systems to develop more effective approaches.

**Drugs for pregnant women**

Pregnant women are evidently one of the most vulnerable groups of malaria patients, but they have the most limited choice of drugs available to them. There have been excellent results from intermittent presumptive treatment with sulfadoxine-pyrimethamine (SP), but once resistance to SP has developed there are very few alternative options. It may also be difficult to justify the cost of introducing a system for provision of SP in pregnancy if the useful life of the drug is very short. Another problem is that not enough is known about the mode of action of the drugs in pregnancy to know the effectiveness of drugs where resistance is already a problem. We do not know much about the effects of short half-life drugs, such a LapDap, in the prevention of malaria in pregnancy, and this may require exploration.

**New options**

Combinations of standard antimalarials with artemisinin derivatives have been covered very nicely by Nick White in his presentation. Other options for new drugs include coartemether, atovaquone-proguanil (Malarone) and pyronaridine as well as recombination of old drugs e.g. chlorproguanil-dapsone (LapDap).

The principle of combination therapy with artemisinin derivatives certainly makes sense. However, combinations of drugs may only delay resistance in certain circumstances where there is a high level of recombination (Curtis and Otoo, 1986). The potential benefits of the gametocytocidal effects may be very great (Price et al, 1996), but the effects on the gametocytes are not fully understood and not all of them are killed (Targett, 1999).

There are a number of operational issues that need to be considered in combination therapy. Ideally the two components should be in one tablet for compliance and ensuring that *both* parts are taken. However the registration of co-formulated combination drugs is time consuming, and so the sooner this process can start the better. The issue of ensuring that both parts are taken if the two components are not in a single tablet needs urgent research; for example examining the role of blister packs. The question of how universally the combinations need to be applied also needs some thought. And then the cost issues are going to be very important, such as who pays and what will be subsidised?

The new drug Malarone is a very effective 3 day treatment, but difficult to synthesize and very expensive. Glaxo-Wellcome has agreed to donate up to one million doses per year, and the Malarone donation programme is working with the Kenyan Ministry of Health to explore its role for SP failures in two districts. The Malarone donation programme is providing useful lessons on the operation of antimalarial drug donation programmes. For instance, in relation to the costs of adding a new drug to policy and the mechanisms for consultation. Pyronaridine is likely not to be available until 2005. Another promising candidate is LapDap, which hopefully will be available by the year 2002.

Both LapDap and SP are antifolates and there is a potential risk that use of SP may generate parasites that are cross-resistant to LapDap. However, LapDap appears to be effective against at least some types of SP resistant parasites. Amodiaquine could be an interim alternative first line combination with artesunsate instead of SP (Watkins, 1998). This may be advisable, but then the cost advantage would be lost. In view of the length of time it takes for a policy change to be implemented, countries should perhaps be working towards gathering relevant information on the alternative options. These are also systems opportunities for improving treatment policy, as better delivery of drugs would actually make a major improvement in the effectiveness of those drugs.

**Conclusions**

So to summarise the needs: What is required in developing drug policy is rationality, as much evidence as possible, communication, financial resources, involvement of all key individuals and obviously the development of new drugs. The initiatives that are going on to address these critical issues include capacity development, improved information systems, the use of social marketing of appropriate treatment, and learning from other diseases. The countries themselves are obviously doing a lot, as well as AFRO and other parts of WHO, the East African Network (EANMAT), Medicines for Malaria Venture, donation programmes, research institutions, and funding agencies.

**Urgent Next Steps**

The situation in East Africa is critical and needs an urgent response. AFRO is in the process of formulating a drug policy framework. This will develop further at a meeting in May 1999 and is a key step in the process of supporting countries. Once there is consensus on the framework, intense activity will be needed in some countries, with external technical support. Funding agencies might consider giving additional resources for relevant data collection and policy development. Generally improving health systems can also have a major impact. And finally there are numerous operational research needs, with an important opportunity for focused research capacity development in African countries. In conclusion, all parties need to think how they can respond to meet the challenge of delivering prompt effective malaria treatment to where it is needed across the African continent.

## Country Priorities and Plans for Chemotherapy for Malaria Control in Africa

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**Background**

The Regional strategies used for control of Malaria in Africa include: case management, vector control and personal protection with emphasis on insecticide treated nets, epidemic preparedness and contrainment as well as operational research to improve the tools that are available. The use of these strategies are dependent on the epidemiology, and human and scientific resource base of each endemic country.

The majority of the African continent is endemic for malaria, with 74% of the population living in highly endemic areas. Therefore, for a long time to come, case management will remain an important strategy for the control of the disease in the African continent. This is because even where there are highly effective vector control programmes, there will still be breakthrough attacks because of low level transmission that will be going on all the time.

In 1994, WHO defined a set of standards for malaria control policies and stated that the primary purpose of effective case management using rational antimalarials is to ensure prompt effective and safe treatment of malaria disease. Effective treatment could however be defined as i) clinical remission, ii) clinical cure and iii) parasitogical cure. For the majority of African countries, the latter goal may be elusive because of the high level of asymptomatic carriers that are already in the population. Therefore, for the primary purpose, an achievable goal would be the clinical cure of the disease. The secondary purpose of rational case management would be to minimise the selection pressure for the development of resistance. Urgent strategies to minimise the appearance of drug resistance to the few effective compounds that are available are needed, if we are not to be confronted with a situation where we would have few options for treatment.

The reasons why chemotherapy or case management has remained one of the important mainstays of malaria control in Africa include the following: it has been found to be cost effective and cheap, and relatively easy to implement on the field in comparison to other strategies. Indeed, the initial capital investment for chemotherapy within a control programme has been demonstrated to be low compared to other measures like vector control. In the long term, the cost to the programme is minimal because the cost is usually borne by the individual patients. The technology associated with case management is not complicated because it involves administration of the drugs concerned, and for the majority of patients, this will be by the oral route. Chemotherapy is usually applicable at different levels of the health care system, and it is not difficult to teach individuals even at the community level how to protect themselves with medicines. Changes in the first line drug does not necessarily mean changes in techniques. With the current on-going health sector reform, chemotherapy appears to be one strategy that can be easily applied even in remote areas, since equity is one of the important goals of health sector reform.

The development of antimalarial drug resistance has however compromised some of the goals and comparative advantages that have been described above. In the field of antimicrobial treatment, resistance has come to stay and will always evolve given time. Therefore, implementors of malaria control should always be one step ahead of the evolution of resistance in their environment. One of the primary strategies that is being employed for chemotherapy is the deployment of rational antimalarial drug policies.

Since 1996, WHO has held a series of meetings in African countries on the problem of rational drug use for the treatment of malaria and the development of antimalarial drug policy. The product that will come out of this cascade of meetings is a rational framework for developing antimalarial drug policies in Africa. This framework has been developed within the concept of health sector reform and the integrated management of disease. This is in line with the

current RBM philosophy which is using malaria to spearhead the management of communicable diseases in Africa.

**Principles for Minimising Drug Pressure**

We are forever confronted with the prospect of the emergence of drug resistance no matter how low the drug pressure in the field. The rate at which resistance will however appear, will depend on the inherent properties of the drug itself, and the extent of pressure to which it is subjected when in use. There are certain principles which implementors should try to uphold in order to reduce the amount of drug pressure on a compound that is deployed for control purposes:

1. New compounds should as much as possible be deployed only in areas where there is documented need.
2. Use the new compound in combination treatment.
3. Maintain strict compliance with treatment regime (give maximal tolerable doses).
4. Ensure strict follow-up of all cases and vigorously treat all recrudescence with alternative sensitive compound.
5. Vector control measures with special reference to personal protection should be vigorously pursued where a new compound is deployed.

**Monitoring Systems**

With the spectre of the emergence of antimalarial drug resistance always before us, it is important that monitoring systems should be established in order that susceptibility to antimalarial drug can be detected early and combative measures instituted. There should be a core group of professionals within the national malaria control programmes who have the responsibility of monitoring the emergence of antimalarial resistance. They should work in collaboration with research institutes so that their techniques can be improved in line with more recent research finding. At the present time, because of the poor relationship between in-vitro susceptibility and in-vivo sensitivity, WHO has recommended the use of the in-vivo method. This does not de-emphasize progress to find cheap and rapid ways of detecting and mapping out resistance. Each control programme should have a database on which the scientific and longitudinal perspective of the sensitivity of antimalarials in common use are placed.

In addition to this, there must be a network of sentinel sites in each country to represent the various epidemiological situations that are present in the country. It should be remembered that for large countries, one or two sites would not represent the current sensitivity pattern.

The national health information systems in each country should be strengthened in order to have a reliable reporting system that would flag decreased clinical usefulness of a drug and possibly be a herald for formal sensitivity studies. The importance of such a reporting system cannot be overemphasized. Indeed, such a system might be the first indication of a much bigger problem. These monitoring systems should be initial data to signal that a change in treatment guidelines may be required.

**Framework for Antimalarial Drug Policy**

Although many African countries have always had vector borne disease control units which are responsibility for malaria control, it was peculiar that, despite the fact that it was known that the mortality and morbidity from malaria was very high, very few African countries had antimalarial treatment guidelines or even had control policies at the beginning of the eighties. This was not unconnected with the fact that the operational research needed to gather the data required for developing these guidelines were usually contracted to bodies other than the Ministries of Health which had the mandate to develop and revise guidelines.

One of the aspects that the Malaria Control Programme at AFRO has developed, is capacity building in some areas that are important for the development of antimalarial drug policies. Specifically, capacity has been built in 31 countries of the continent in therapeutic efficacy test. In addition to this, WHO has produced guidelines for carrying out these studies at the

district level. In these countries, sentinel sites have been set up so that each country could have data bases that would provide scientific longitudinal perspectives of the problem of sensitivity to the commonly utilised antimalarials in the individual countries.

WHO has gathered experience in assisting countries with the provision of rational malaria treatment guidelines. In the first place, there must be evidence for the update of a policy. This will be in the form of formal efficacy studies, studies on the efficacy of the putative first line drug, with data on the economic advantages of changing from the current first line drug. At the time when the treatment guidelines are being changed, the policy makers should be very careful to make sure there is participation of all the stakeholders that are involved in the process. One of the ways in which this can be achieved is to set up a multi-disciplinary body to supervise the implementation of the process. At this stage, indicators for monitoring and evaluation of the process should be developed so that instruments for constant monitoring and evaluation may be put in place. Operational research issues will be one of the priorities of this multi-disciplinary body to ensure that operational questions are answered as the process goes on.

**Operational Research for Combination Therapy**

As policies are updated or changed, depending on the circumstance of each country, the options that are open for case management of the uncomplicated disease will diminish. Unfortunately, in the field of malaria chemotherapy, there are few options open as substitute for the currently used first-line antimalarial drugs. There is wide-spread chloroquine resistance, and increasing resistance to sulfadoxine pyrimethamine which is the drug that many countries are hoping will replace chloroquine.

Since combination therapy is a well known strategy to slow down the emergence of resistance to an antimicrobial compound, there is much interest in the development of rational combination treatment regimes using different principles to slow down the emergence of drug resistance. This is an area of great focus for the TDR. At the present time, a region wide combination trial of various compounds with the artemisinin compounds are going on in order to obtain a “proof of principle” for combination therapy in areas of intense transmission. Following these series of investigations, the studies will be done to find out the effect of wide scale use under implementation and control conditions on 1) rate of emergence of resistance, if at all and 2) the effect of the combination on the burden of disease.

These are very exciting and promising times in the various studies that are going on in relation to chemotherapy in the continent. One aspect that is obvious would be how to accommodate the rapidly changing scenario within the concept of a rational antimalarial drug policy for the countries of the region.

**Approaches to Chemotherapy**

Several opportunities have opened up for the effective implementation of case management of malaria at different levels of the health care system. One of the most important opportunities for case management of malaria for children five years and below is the IMCI approach. Within the region, more than 20 countries have now adopted the IMCI approach to the management of febrile diseases. A recent monitoring visit to Tanzania by a joint WHO/DFID team demonstrated that the IMCI approach improved the skill of health care personnel trained in case management. It also showed an increase in the number of attendances at health care centres due to improvements in disease management and relations with the consumers. Many countries within the region are making the approach a priority programme to tackle the menace of high childhood mortality and morbidity. It is expected that, as new tools for example combination therapy for the treatment of malaria disease come up, they will be incorporated into the IMCI approach.

The IMCI approach has three aspects. First is case management which has a syndromic approach. By rational utilisation of common symptoms and signs, putative diagnosis of the common febrile illness are made. Management is then carried out within the limits of the

national guidelines for the particular illness. Follow-up and counselling are important aspects of case management using the IMCI approach. With over 40% of childhood fevers being attributed to malaria in endemic areas, the importance of the IMCI approach for the management of malaria cannot be overestimated.

The second aspect of the IMCI approach that is very important to case management is community management of disease. It is known that the majority of deaths in the Region take place at the community level. Therefore, by utilising this approach in IMCI, it is expected that the philosophy of early diagnosis and prompt treatment of illness will be better realised. Finally, IMCI aims to use its approach to tackle the problem of health systems. IMCI will address the issues of costs of implementation, the drug supply management organisation of work at the health facility level, problems with support systems and the problem of referral.

The last aspect of IMCI is the question of the approach and how it will influence health systems. This is important, as challenging changes are taking place in our health systems in the continent with cost of the approach, sustainability, user fees, and referrals being aspects that the IMCI approach expects to positively influence. We can therefore see that the IMCI package has a lot to offer in terms of case management for children under the age of five years.

The malaria programme itself has adopted as one of it major strategies, community management of the disease. The thrust of this strategy is to use workers within the communities to make rational decisions on the drug treatment of fevers in all age groups, whilst ensuring that the commonly used first line drugs are available. Referral systems will be examined for each situation. This approach would, in the long run, assist with the much-needed reduction in mortality from malaria in the region where it is effectively carried out. The catchment population for each community is all persons that are at risk for malaria disease.

Since women in the reproductive age group form a significant proportion of the population in the continent, and pregnant women are more prone to developing problems associated with malaria disease, the reproductive health programme will be one channel that would be used to ensure that women in the child bearing age group are catered for. In addition to this, the region is in the process of re-evaluating its policy for prophylaxis and the management of malaria in pregnant women. This would not be an easy task in the face of rising antimalarial drug resistance, dwindling resources, poverty and inequity in the region, especially in this instance with respect to women.

**Implementation Challenges**

The operational challenges to case management will become more difficult with the passage of time. The experience in the region has been that there is no easy path to updating policies, because they affect people and society. As we change first-line drugs, the cost to the programme will have to be carefully evaluated. This is because all the proposed new compounds are multiples of the cost of chloroquine, which is arguably currently the cheapest antimalarial. In the final analysis, the cost of treatment will be mostly borne by the patient, which may further aggravate the problem of inequity. A situation where only a small segment of the society is able to afford antimalarial drugs should not be encouraged as the disease knows no boundaries.

Changes in drug treatment are often accompanied by the problems of acceptability of the new regime. Changes from Chloroquine to SP have often been resisted on the part of the providers and consumers who may feel that SP is an “inferior” drug. The social perspectives of all antimalarial drug treatments have to be carefully managed. Compliance to the new regime may not be fully divorced from social acceptability. This is because where the regime for treatment is difficult to follow, there would be problems with drug pressure. Where two or even three compounds are required, then the problem of compliance would be even further exaggerated.

It is important that as we move from mono-therapy to combination therapy, the mode of delivery of the drug should be simple. This is more important for delivery through infusions in the case of severe disease. Where the delivery mode is not simple, it is not likely that the new regime will be rationally used in the peripheral area where the majority of the population live with grave consequences for the development

The question that always confronts implementors are these: will the drug reach the majority of the people; will they be able to afford it; how soon will resistance appear; and if resistance does appears, is there an alternative? These are not easy questions to answer.

**Collaboration**

Successful implementation of the malaria control strategy in the region will depend on a number of factors, an important one being collaboration with partners. These partners are themselves implementors. Therefore, WHO should be a brokering partner to ensure that partners follow national antimalarial drug policies. Where policies are not adhered to, a chaotic situation emerges which introduces complex drug pressures on the field with totally unpredictable results. The few antimalarial compounds that we have are so precious to us, that all partners should collaborate to avoid the situation where a chaotic scenario emerges.

Industry has often been ignored in the process of developing drug policies and treatment guidelines. The complex situation of emerging resistance makes it imperative to involve industry early in the process of change. Industry has a lot to offer in the areas of costing, packaging and fundamental research that may restructure the whole way in which we perceive case management.

**Concluding remarks**

The importance of chemotherapy to malaria control programmes will continue to increase, bearing in mind the epidemiology of the disease and the increase in the spread of malaria in the African Region. New approaches to case management in the African Region have to be opened up if we are to meet the current challenges that face us in this Region. New research to find drugs, either singly or in combination, that may reduce the burden of disease, are currently needed. This of course will be in addition to the use of other techniques such as personal protection and vector control. It is a combination of various strategies that will ultimately reduce the high mortality in the short- and medium-term, and high morbidity in the long-term, that have for so long been the scourge of malaria in the African Region.

## Collaborations to Address the Challenge of Antimalarial Drug Resistance

Peter Bloland, Centers for Disease Control and Prevention, Atlanta, USA

The last few years have produced a significant surge in interest, energy and resources aimed at malaria. Along with this increased interest and enthusiasm, there has been increased recognition of the benefits of broad collaboration and willingness to enter into collaborations with a variety of new or nontraditional partners. Collaboration has played a key role in the area of antimalarial drug resistance in the past and will be essential to effectively meeting this growing challenge in the future.

For the next few minutes, I would like to talk about three truly multilateral collaborations that CDC has had the pleasure to participate in, two that have been ongoing for a few years, and a third that is just beginning to be put into place.

One of the interesting characteristics of all of these activities is that the involved partners did not necessarily start out with the intent to collaborate, but rather they came together through a realisation that the scope and nature of the problem of drug resistance was such that no single group could succeed on its own, a recognition that others shared their goal and commitment, and an acknowledgement that each group had something unique and important to contribute to the effort.

The first was an effort that brought together components of WHO, CDC, USAID and a number of ministries of health and medical research institutes in Africa, to develop a standardised protocol for assessing antimalarial treatment *in vivo.*

Granted, this was not a new concept. Standardised protocols had been developed in the past and the fact that nearly everyone in this room can recite the definition of RI, RII, and RIII attests to the wide spread use of these protocols over the years.

Reviewing reports of studies using these standardised methods published over the last 10 years, a picture can be generated that illustrates the status of antimalarial drug resistance in Africa. But, unfortunately, it is not a picture without significant problems.

The first major problem is a methodological one: the extent to which, over the years, this methodology has been modified. Modifications have been so extensive and so different between researchers, sites, and years that it is not unusual to find two separate evaluations of the same drug conducted in the same area during the same year that yield results that support dramatically different and conflicting interpretations.

The second major problem is a functional one: the results of studies using this methodology have not been highly successful in motivating change in malaria treatment practices in Africa. There are many reasons for this, but one of the most important reasons is that while these methods gave reasonable data about how healthy parasites respond to antimalarial drugs, they gave little information about how sick people respond to malaria treatment. This limited the potential programmatic impact of the data collected over the years. So while an interesting picture can be made, it is difficult to know what to make of the interesting picture.

**The goals that have developed within this collaboration were:**
First, to design a programmatic tool for collecting highly comparable information on the current efficacy of malaria treatment options across the region, and second, to allow more reliable comparisons of information across time and geography. To do this successfully, the new protocol needed to have outcomes that reflected and focused on patient responses to treatment, to be relatively simple in design so that people not coming from a research background could easily be trained in the methods, and to be sustainable in terms of the time and resource investments required.

The result of this collaboration is a protocol that goes a long way towards fulfilling these objectives. WHO-AFRO, a critical partner in the development of the protocol, has since been exceedingly busy in training control programs in the methodology and supporting its use throughout Africa.

The early results of these efforts are promising in terms of the amount of highly comparable data collected in a short period of time. Again, one can begin to piece together a picture of the current status of malaria treatment in Africa, but with a major difference. This time, because a truly standardised methodology was used throughout, the picture is one that we can easily interpret and use with confidence. Over time, provided these methods can withstand people's natural inclination to modify, this picture will become more detailed.

But collecting data on response to antimalarial treatment is not an end in and of itself. To be useful, information must be used. Once again, a collaborative effort developed out of a shared recognition of need. Many of the collaborators who worked together on the standardised protocol were joined by new partners, notably DfID and the Wellcome Trust, in investigating how information is used in antimalarial drug use policy development and decision making.

There were three primary observations that drove this collaborative effort.

1. It became apparent that antimalarial treatment recommendations lagged behind the actual status of antimalarial drug resistance.
2. Parasitologic resistance data and biomedical arguments for policy change alone did not appear to be sufficient evidence in the eyes of decision-makers to warrant major policy change.
3. Although we knew quite a lot about those biomedical arguments, collectively we know little about other influences on the process of policy-level decision making or about the process of decision-making itself.

**The general goals of this collaboration were:**

- To elucidate the relevant inputs that go into the process of developing policies that seek to address drug resistance and malaria therapy;
- To encourage more active participation of representatives of other disciplines in the policy dialogue especially behavioural scientists, economists, and the private sector;
- To improve the understanding of the decision making process itself; and
- To utilise this information to improve countries' ability to effectively address the challenge of antimalarial drug resistance as well as to improve the international community's ability to assist and support this process.

Towards these ends, a number of agencies co-sponsored a series of workshops on antimalarial drug use policy development that included over 60 participants from 23 countries. An important aspect was the inclusion of representatives from both the research community *and* the programmatic community.

The objectives of these workshops were to discuss options and approaches to meeting the challenge of drug resistance in Africa, and equally important, to identify and discuss important inputs to the process of developing proactive drug use policies.

In additional to the biomedical inputs so frequently and extensively investigated in the past, the other important inputs identified and discussed at these workshops included:

- Epidemiologic inputs - especially regarding the public health impact of resistance such as has been discussed earlier by Jean-Francois Trape;
- Socio-behavioural inputs - issues like treatment seeking behaviour, acceptance of policies and treatments, and compliance with recommendations not only on the part of patients, but also on the part of providers;
- Political inputs - from the level of political will within a given country to the complex interrelationships between public health and other important public policy components;
- Economic inputs - including costs and cost-benefits;

- Legal-regulatory inputs - including how new drugs are introduced into a country and what countries can do to encourage appropriate use though regulatory systems;
- A large group of cross-cutting issues including the role and influence of international pharmaceutical companies and the local private sector.

These workshops were merely one step in a long process, but highlighted the fact that, without a level of attention and understanding of these inputs equal to what we have applied to understanding how parasites respond to drugs, moving towards the ultimate goal of improved case management and limitation of the impact of drug resistance will be difficult, if not impossible.

Now that we have what we hope is a useful and useable method for assessing antimalarial treatment efficacy as well as an improving understanding of how to use this and other information to develop policies and practices to address the threat and reality of drug resistance, many have recognised a need to monitor changes in drug resistance and hopefully, the impact of drug use policies on the spread and intensification of resistance across the region.

To do this, another collaborative effort is proposing to create a surveillance system for tracking changes in antimalarial drug resistance in Africa. Although specific contributors to this effort can be identified as I have attempted to do here, the ultimate success of this proposed collaboration really rests on the participation of everyone in Africa involved in antimalarial drug efficacy testing. This will truly need to be a region-wide, all-inclusive collaboration.

**The goals of this proposed collaboration are:**

- To create a unified, single source surveillance system for drug efficacy data for all of Africa;
- To tract temporal and geographic trends and to link these data to other available malaria data;
- To make these data readily available to all who need or have an interest in them; and
- To use this activity to continue to build capacity of participant institutions and individuals in Geographic Information Systems, efficacy testing and surveillance methodology.

To do this, the partners are proposing to build on the existing infrastructure and methodology of the MARA project to create a “network of networks” with all those who are engaged in efficacy monitoring. In order to return the information collected to all who wish to use it, we are proposing to develop information dissemination systems that also build on existing resources as well as to provide reports on antimalarial drug resistance tailored to specific uses, countries, sub-regions, and Africa as a whole.

In conclusion, while there are certainly many more collaborative efforts that have been or will be discussed during this meeting, these few examples illustrate how, working together, significant contributions to the fight against antimalarial drug resistance can be made. The enthusiasm and interest in developing new collaborations to address specific issues in malaria and the willingness to welcome new voices and opinions into the effort is exciting, and I think we all look forward to hearing about their successes in the future.

## BREAKOUT SESSIONS: ANTI MALARIAL DRUGS

### Programme

**1. Meeting Challenges with Antimalarial Drugs in Africa.**
Chair: Dr. Don Krogstad and Professor Ayoade Oduola
Rapporteur: Olumide Ogundahunsi, A. Akanmori, Catherine Falade

**Presentations (15 mins each)**
1. Needs and priorities for effective utilisation of antimalarial drugs in Africa - Tom Sukwa.
2. Process and Implications of Drug Policy Change for Malaria Control.
   - Malawi experience - Peter Kazembe.
   - Kenya experience - Beth Rapouda.
3. Integrating *in vitro* and *in vivo* Drug Sensitivity Monitoring in Malaria Control: Experience.from Mali -
   Ogobara Doumbo and Chris Plowe.

**Abstract Presentations (5 mins each)**
1. Molecular epidemiology of drug resistance: Suitability of assays for surveillance under the MIM network in Africa - Chris Plowe.
2. Needs assessment for the development of drug policy for front line health workers - Amos Odhacha.
3. Establishing malaria treatment policies in Burundese refugee camps in western Tanzania 1998 - Holly Ann Williams.
4. Monitoring the efficacy of sulphadoxine/pyrimethamine in falciparum malaria around Muheza, Northeast Tanzania - Martha Lemnge.

**Discussion 15 minutes**

**2. African Scientists and Institutions in Developing Drugs for Malaria.**
Chairs: Dr. Wilbur Milhous and Dr. John La Montagne.
Rapporteurs: Christian Happi, Grace Gbotosho, Wilfred Mbacham

**Presentations**
1. Drug development Needs and Resources - Dennis Kyle (20 mins).
2. Drug Registration Policy - Peter Folbe.
   New Initiatives for Malaria Drug Discovery
3. New Medicines for Malaria Venture - Rob Ridley (15 mins)
4. Harvard Malaria Initiative - Dyann Wirth (10 mins)
5. An overview of Potentials and Resources available in Africa - Bill Watkins (10 mins).

**Panel Discussion: Perspective on Political, Practical and Economic Implications of Integrating African Scientists and Institutions in drug development for Malaria.**
Moderator: Dr. Rob Ridley
Rapporteurs: Dr Wilfred Mbacham, Dr. Grace Gbotosho and Dr. Stephanie James
Panel: Dr. Bill Watkins, Dr. Dennis Kyle, Dr. Carlos Morel, Professor Dyann Wirth (5min), Dr. John Horton (5min), Dr Michael Gottlieb.

**3. Joint Session: Management of Severe Malaria and Antimalarial Drugs**
Chair: Dr. Pascal Ringwald and Dr. Piero Olliaro
Rapporteur: Dr. Didier Diallo, Dr. Dora Akinboye, Dr. Eric Achidi

**Presentations (20 mins)**
1. Implications of drug resistance and loading dose in treatment of severe malaria in Africa - Akintunde Sowunmi.
2. Current practices and Potential Role of antimalarial suppositories in management of severe Malaria in Rural Areas - Melba Gomes.
3. Meta-Analysis of arthemether and quinine trials in management of severe malaria - Nick White.

**Abstracts (5 min each)**
1. La quinine en solution intrarectale est efficace dans le neuropaludisme et les acces graves de l'enfant en Afrique - Hubert Barennes.
2. Artesunate suppositories in the treatment of moderately severe malaria in Malawian children - Madalitso Tembo.
3. A randomised, placebo controlled, double-blind study of the tolerability and efficacy of Artesunate plus sulphadoxine/pyrimethamine combinations vs. Single-agent sulphadoxine/pyrimethamine for the treatment of uncomplicated falciparum malaria - Lorenz von Seidlein.
4. Comparative efficacy of chloroquine and co-trimoxazole in acute uncomplicated falciparum malaria in children - Adegoke Falade.

## Summary Report: Antimalarial Drugs

### Management of Severe Malaria and Anti-Malaria Drugs – Joint Session

Chair - Dr Piero Olliaro
Rapporteurs: Drs D. Diallo, D. Akinboye and W. Mbacham

**Research priorities**

- Investigate unmet applications of new drug formulations to reduce evolution to and mortality due to severe malaria.
- For uncomplicated malaria, the identification of effective drug combinations which may delay or reduce the establishment of drug resistance.

**Implications of Results for Control**

**Artemether-Quinine Meta-analysis study**

- Artemisinin derivatives are still the most rapidly acting anti-malarials
- A meta-analysis study in both adults and children of 7 randomized trials in severe malaria show that Artemether tended to achieve more rapid parasite clearance and was significantly better in some subset analyses but overall, was not significantly better than quinine in reducing severe malaria mortality.
- A significant improvement in terms of lives saved cannot be expected in Africa upon introducing Artemisinin-type compounds based on available evidence and current quinine efficacy. However, these results show that Artemeter can be expected to be as good as quinine and potentially better in case of quinine resistance. A reduction in mortality should then rather be sought in earlier, nearer-home interventions

**Alternative Forms of Drug Administration**

- Intra-rectal use of quinine solution was effective in children with moderate neurological symptoms and in severe malaria, and may serve as an alternative for intra-muscular or infusion quinine treatment especially when a child has not got diarrhea. Further research is needed on formulations.
- Rectal Artesunate was effective for emergency treatment of moderately severe malaria with reduction in parasite density and fever. Single dose rectal Artesunate must be followed by an effective parenteral or oral treatment. A dossier for registration will be submitted by the WHO soon.

**Multi-drug Therapy**

- **Chloroquine and Co-trimoxazole** in acute uncomplicated *falciparum* malaria in children, in Nigeria were equally effective individually in reduction of fever and parasite clearance time. No difference was found between 3-day and 5-day treatment courses with Co-trimoxazole. While this could offer options for treatment, of children with overlapping symptoms of malaria and respiratory infections, the implications in terms of parasite and bacterial resistance generation are not known

- A combination of **Fansidar and Artesunate** (1 and 3 doses) resulted in faster parasite clearance and faster disappearance of gametocytes with respect to Fansidar administered alone. Gametocytes were still infective in mosquitoes 4-7 days post-treatment. The problem that remains to be solved is to investigate the difference between gametocyte persistence upon treatment with Fansidar and the Fansidar-Artesunate drug combination. This was one of a series of multi-center studies due to enroll several thousands patients across Africa.

- Examples of combination of **Chloroquine and Resistance Modifiers** requires multiple administration over seven days. Though impractical, they represent a “proof of concept” that resistance can be reversed *in vivo*.